



Doc Code: AP.PRE.REQ

PTO/SB/33 (07-05)

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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) CARP0006-100	
<p>I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on <u>June 22, 2006</u></p> <p>Signature <u><i>Doreen Yatko Trujillo</i></u></p> <p>Typed or printed Name <u>Doreen Yatko Trujillo, Reg. No. 35,719</u></p>		Application Number 09/719,045	Filed December 7, 2000
		First Named Inventor Andrew P. Chapman et al.	
		Art Unit 1644	Examiner David A. Saunders
<p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p>			
<p>I am the</p> <p><input type="checkbox"/> applicant/inventor.</p> <p><input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)</p> <p><input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>35,719</u></p> <p><input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number _____</p>		<p><u><i>Doreen Yatko Trujillo</i></u> Signature</p> <p><u>Doreen Yatko Trujillo</u> Typed or printed name</p> <p><u>(215) 665-5593</u> Telephone number</p> <p><u>June 22, 2006</u> Date</p>	
<p><input type="checkbox"/> *Total of _____ forms are submitted.</p>			

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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DOCKET NO.: CARP0006-100

PATENT

APPLICATION SERIAL NO. 09/719,045

AMENDMENT AND REQ. FOR RECONSIDERATION DATED JAN. 9, 2006

REPLY TO OFFICE ACTION OF JULY 8, 2005



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Chapman and King**

Confirmation No.: **3379**

Serial No.: **09/719,045**

Art Unit: **1644**

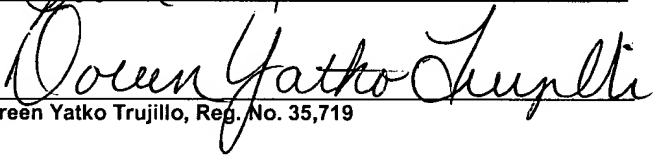
Filed: **December 7, 2000**

Examiner: **David A. Saunders**

Title: **DIVALENT ANTIBODY FRAGMENTS**

Customer No.: **34133**

I, **Doreen Yatko Trujillo**, Registration No. **35,719** certify that this correspondence and accompanying papers are being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the U.S. Patent and Trademark Office, Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

On June 22, 2006

Doreen Yatko Trujillo, Reg. No. 35,719

MAIL STOP AF

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Dear Sir:

ARGUMENTS ACCOMPANYING PRE-APPEAL BRIEF CONFERENCE REQUEST

Pursuant to the Official Gazette Notices dated July 12, 2005 and February 7, 2006, Applicants hereby request a Pre-Appeal Brief Conference. A Notice of Appeal accompanies this request. This request is being filed in response to the Final Rejection dated as mailed March 29, 2006. Accordingly, it is believed that no extension of time is necessary. If Applicants' belief is erroneous, Applicants hereby petition for any necessary extension, and authorize that any fee for said extension be charged to Deposit Account 50-1275.

Claims 1-15 are pending. Claims 1-10 and 12-15 remain rejected. Briefly, the claims are directed to divalent antibody fragments, having two heavy chains, attached to a polymer

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molecule, wherein the polymer molecule is covalently linked to a cysteine residue outside of the variable region domain **on each heavy chain** of the divalent antibody fragment through a non-disulphide interchain bridge. Such cysteine residues are normally involved in disulphide interchain bridges through sulphur atoms on the cysteine residues.

Two rejections remain. Both rejections were levied over U.S. Patent No. 6,025,158, issued to Gonzalez et al. on February 15, 2000, claiming priority to February 21, 1997, as the primary reference ("Gonzalez"). Claims 1-10, 12-13, and 15 were rejected under 35 USC 102(e) or, in the alternative, under 35 USC 103(a), over Gonzalez. Claims 1 and 13-14 were rejected under 35 USC 103(a) over Gonzalez, in view of U.S. Patent No. 5,436,154, issued to Barbanti et al. on July 25, 1998. Gonzalez, however, does not disclose or suggest Applicants' invention. More specifically, Gonzalez does not disclose or suggest a divalent antibody fragment having a polymer molecule covalently linked to a cysteine residue outside of the variable region domain **on each heavy chain**. Barbanti et al. does not overcome this deficiency.

To maintain a rejection under 35 USC 102(e), the Office must rely upon inherency to supply the missing claim element highlighted above, i.e., that the polymer is covalently linked to a cysteine residue on each heavy chain. The Office, however, is misapplying the inherency standard. This misapplication of inherency is a clear error. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient." MPEP 2112, IV, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999), emphasis added.

As the Office correctly notes, Gonzalez describes a polymer molecule used to link together two antibody fragments in a "dumbbell-shaped structure" (col. 35, lines 40-57). And, Gonzalez describes the attaching of a polymer to the hinge region of a parental antibody fragment (not two antibody fragments), preferably via cysteine residues that have been engineered into the fragment (col. 19, lines 35-55). What Gonzalez does not describe, however,

is a polymer molecule specifically linking **two** antibody fragments through a cysteine residue on the heavy chain of **each** fragment, i.e., the subject matter of claim 1, to form that dumbbell shaped structure.

In the Final Rejection, the Office admits that the coupling of the polymer to free cysteines in the hinge region was not mentioned where Gonzalez teach the dumbbell shaped structure, but argues that “coupling Fab’ to PEG via the cysteine residue of the Fab’ heavy chain is clearly within the 4 corners of the reference” and that, “[a]t the least, one would have found it obvious to couple the later exemplified Fab’ having an available cysteine residue in the hinge region of its heavy chain to PEG via the SH group of the cysteine, in order to form the dumbbell shaped structure.” (See the Final Rejection, paragraph bridging pages 2-3). That individual elements may be found “within the 4 corners of the reference,” is not the standard for inherency, however. While it may be **possible**, based upon the teachings in Gonzalez, to prepare an antibody fragment as claimed, inherency is not established by possibilities. It must be shown that such antibody fragments are necessarily described in Gonzalez; they are not.

Neither is “within the 4 corners of the reference” the standard for obviousness, the Office’s conclusory statement notwithstanding. To establish a *prima facie* case of obviousness, the Office must show, *inter alia*, motivation to modify the reference to result in Applicants’ invention. MPEP 2142, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Office has not done so. Indeed, there is no motivation, absent Applicants’ disclosure, to prepare such an antibody fragment. Thus, not only has the Office erred in its application of inherency, but it has failed to establish a *prima facie* case of obviousness.

Further, as Applicants argued previously, Gonzalez actually teaches away from the antibody fragments as claimed. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). When Gonzalez is considered as a whole, it leads away from Applicants’ invention. First, Gonzalez suggests making dumbbell structures using polymer molecules derivatized with

“**multiple functional groups**” to permit the attachment of two or more antibody fragments to the polymer backbone. See column 35, lines 45-57. The use of multiple functional groups suggests multiple attachment locations, not the same location on each heavy chain, much less a cysteine residue on each heavy chain. Indeed, Gonzales et al lists a variety of crosslinking sites on the antibody fragments that can be used, e.g., N-terminal amino groups and epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (See column 41, lines 63-57). The Office, in the Final Rejection, accuses the Applicants of obfuscating the issues by pointing out these other teachings of Gonzalez. Applicants are not obfuscating the issues by relying upon all the teachings of the reference but, rather, following legal precedent.

Second, when Gonzales discusses attaching an $F(ab')_2$, i.e., a divalent antibody fragment, to a polymer, it specifically teaches that disulfide bridges are avoided by **substituting** another amino acid for the corresponding **cysteine** residue in the opposite chain. See, for example, column 21, lines 50-59; column 23, line 29 through column 24, line 27; and column 31, line 55, through column 33, line 17 of Gonzalez. The Office alleged that Applicants were highlighting one genre of embodiments while ignoring another. Such an argument would have more force if Applicants’ invention were actually disclosed as an embodiment in Gonzalez; as the Office acknowledges, however, it is not. Further, Applicants are highlighting the most relevant genre in Gonzales, i.e., that of divalent antibody fragments connected to polymers. Regardless, the Office cannot just consider those aspects of the reference that support its position. The reference must be considered as a whole. It is error to do otherwise.

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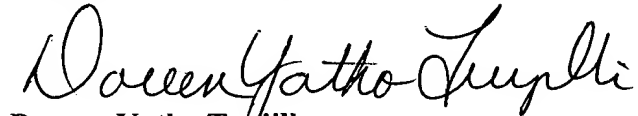
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In summary, Applicants respectfully submit that the Office made clear errors and/or omitted one or more essential elements needed to establish a *prima facie* rejection.

Respectfully submitted,



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Date: June 22, 2006

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